REMARKS

Claims 1-4, 7-10, 28 and 32 were pending in this application. Claim 28 has been amended. No new subject matter has been added by this amendment. Claims 5, 6, 11-27, 31 and 33-81 were previously canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof. Accordingly, Claims 1-4, 7-10, 28 and 32 remain in this application.

35 U.S.C. § 112 Rejection

Claim 28 stands rejected under 28 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement by including subject matter which was not described in the specification in such a way so as to enable one skilled in the art to make or use the invention. For brevity, reference is made to page 3 of the Office Action for the complete reasons for rejection.

Although Applicants respectfully disagree with and traverse this rejection, claim 28 has been amended to expedite examination of this application, without prejudice, to remove the language "or prevention" from the claim. Accordingly, Applicants respectfully request the rejection of claim 28 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

35 U.S.C. § 103 Rejection

Claims 1-4, 7-10, 28 and 32 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,698,527 ("Kim et al.") and WO 0038725 ("Keller"). The reasons for rejection are set forth in the Office Action, summarized as follows:

It is asserted that Rosenblum et al. teach the instant cholesterol absorption inhibitors, their application for lowering serum cholesterol and combination with other cholesterol lowering agents such as simvastatin. Office Action at page 5. Further, it is asserted that Rosenblum et al, teach a daily dosage in a range of 5 mg to 1000 mg a dose given 1 or two times a day and that the exact dose would depend upon various conditions. Office Action at page 5.

It is acknowledged that Rosenblum et al. do not expressly teach a combination of a cholesterol absorption-inhibitor, such as ezetimibe, and a nicotinic acid. Office Action at page 5.

In the rejection, it is alleged that Kim teaches that niacin is a well-known cholesterol lowering agent and is particularly useful in combination with cholesterol absorption inhibitors. Office Action at page 5. It is further alleged that Keller et al. teach various combinations of cholesterol lowering agents, including ezetimibe and nicotinic acid, for treating hypercholesterolemia-associated disorders. Office Action at page 5.

It is alleged that it would have been obvious to one of ordinary skill in the art, at the time that the claimed invention was made, to make a composition comprising ezetimibe and nicotinic acid, and optionally simvastatin, citing In re Kerkoven, 205 U.S.P.Q. 1069. Office Action at page 5.

It is further alleged that the specific amount of 10 mg is within the range disclosed by Rosenblum et al. Office Action at page 6.

In view of the following remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

The law is replete with cases holding that there must be some suggestion or motivation in the prior art to combine the references. When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

The present invention is directed to a composition and therapeutic combination of at least one nicotinic acid or derivative thereof and about 10 milligrams of at least one sterol absorption inhibitor, represented by Formula (II) (ezetimibe) in the present application, for the treatment of vascular condition, diabetes or obesity.

As shown in Table 1 of the present application, Compound XII (a substituted azetidinone cholesterol absorption inhibitor) reduced plasma cholesterol levels and the accumulation of hepatic cholesteryl esters in the cholesterol-fed hamsters. Niacin reduced plasma triglyceride levels, but did not significantly reduce the cholesterol levels. The combination of Compound XII and niacin resulted in reductions in plasma and hepatic cholesterol levels, as well as plasma triglycerides (Table 1). These results indicate that the combination of the cholesterol absorption inhibitor of Compound XII and niacin can have additive effects on treating hyperlipidemia in male Golden Syrian hamsters, by reducing both cholesterol and triglyceride levels. One skilled in the art would understand that the compatibility and efficacy of drug combinations can be unpredictable.

The Office Action contends that Rosenblum et al. teach the instant cholesterol absorption inhibitor, its application for lowering serum cholesterol, and a daily dosage of the compounds in a range of 5 mg to 1000 mg if given in a single dose or 2-4 divided doses, and when used in combination with other cholesterol lowering agents, a dosage of 1 mg to 1000 mg a dose if given one or two times a day, also noting that the exact doses would depend upon various conditions. Rosenblum et al. disclose cholesterol absorption inhibitors, used alone or in combination with simvastatin, and their application for lowering serum cholesterol. However, the Action recognizes that Rosenblum et al. do not suggest or disclose the combination of cholesterol absorption inhibitors with nicotinic acid. In addition, Rosenblum et al. do not suggest or disclose

the desirability of a 10 milligram dosage of ezetimibe. Further, Rosenblum et al. do not suggest or disclose lowering of triglyceride levels.

The Office Action contends that Kim teaches that niacin is a well-known cholesterol lowering agent and is particularly useful in combination with cholesterol absorption inhibitors. Kim discloses steroidal glycoside cholesterol absorption inhibitors that can be administered in combination with niacin, however, Kim does not suggest or disclose combining ezetimibe with niacin or the desirability of the claimed amount of 10 milligrams of ezetimibe. Ezetimibe is not a steroidal glycoside. The steroidal glycosides disclosed by Kim are structurally very dissimilar to the presently claimed substituted azetidinone compound ezetimibe. One skilled in the art would not be motivated to substitute ezetimibe for steroidal glycoside since their molecules are so structurally dissimilar.

Moreover, given their large molecular size, it is unlikely that Kim's steroidal glycosides are absorbed through the intestine. In contrast, multiple peaks in plasma concentration-time profiles suggest that the glucuronide conjugate of ezetimibe undergoes enterohepatic recycling before elimination. See ZETIA™ (ezetimibe) Tablets Package Insert at column 2 (Merck/Schering-Plough Pharmaceuticals) (October 2002), included in the Information Disclosure Statement of August 30, 2004. This enterohepatic recycling can enhance efficacy. It would not be obvious to one of ordinary skill in the art to substitute ezetimibe disclosed by Rosenblum et al. for the steroidal glycosides disclosed by Kim, since they are likely to be dissimilar in site of action.

Kim's steroidal glycoside compounds have not been commercialized by Merck & Co., Inc. (the assignee of the Kim patent). Rather, Merck is the joint venture partner of Schering-Plough (assignee of the present application) in marketing the cholesterol absorption inhibitor ZETIA™ ezetimibe formulation. ZETIA was launched in late 2002 and global sales of ZETIA in the 2003 fourth quarter totaled $165 million, with U.S. sales of $144 million. Press Release: Schering-Plough Reports Financial Results for 2003 Fourth Quarter, Full Year (Monday January 26, 6:33 am ET). Thus, it can be

inferred that Kim's steroidal glycoside compounds, administered alone or in combination with niacin, were not commercially viable as treatments.

"[S]econdary considerations such as ... commercial success, long-felt need, failure of others ... are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence." M.P.E.P. § 2141 (Rev'd May 2004). Applicants respectfully request that the above information regarding commercial success, long-felt need, and failure of others be considered by the Examiner.

No data is presented in the Kim reference to support efficacy of a combination of steroidal glycoside and niacin. One skilled in the art would not be motivated to combine ezetimibe and nicotinic acid based upon the disclosure of Kim since the steroidal glycoside and ezetimibe molecules are so structurally dissimilar.

The Office Action contends that Keller et al. teach various combinations of cholesterol lower agents, including ezetimibe and nicotinic acid, for treating hypercholesterolemia-associated disorders. However, Keller et al. disclose combinations of (1) an ileal bile acid transport inhibitor or CETP inhibitor and (2) a cholesterol absorption inhibitor, such as ezetimibe, or nicotinic acid. However, Keller et al. does *not disclose the combination of ezetimibe and nicotinic acid.* Also, Keller et al. does not suggest or disclose the desirability of a 10 mg dosage of ezetimibe.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in any of the cited references, taken alone or combined as advocated in the rejection, to combine the claimed components of 10 milligrams of ezetimibe and nicotinic acid. Even if the teachings of the references were combined as set forth in the Office Action, there are not sufficient teachings to motivate one of ordinary skill in the art to pick and choose among thousands of compounds to combine 10 milligrams of ezetimibe with nicotinic acid. Neither Rosenblum et al., Kim, nor Keller et al., taken alone or combined as set forth in the Office Action, provides motivation for combining 10 milligrams of ezetimibe and niacin.

Also, Applicants respectfully request that the above information regarding commercial success, long-felt need, failure of others be considered by the Examiner.

Applicants respectfully assert that the rejection is based upon improper hindsight reconstruction. The prima facie case of obviousness has not been established. Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1-4, 7-10, 28-30 and 32 be reconsidered and withdrawn.

Respectfully submitted,

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